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Title:

Optical coherence tomography angiography (OCTA) findings in Dengue-related maculopathy: A case report.

Authors:

S. Tavassoli,[1] E. Carreno,[1,*] S. Teoh,[2,3] S. Theodoropoulou,[1] C. Bailey,[1] RWJ. Lee,[1,4,5] AD. Dick. [1,4,5]

[1] Bristol Eye Hospital, University Hospitals Bristol NHS Foundation Trust, Bristol, UK.

[2] National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore.

[3] Eagle Eye Centre, Mt Alvernia Hospital, Singapore.

[4] School of Clinical Sciences, Faculty of Medicine and Dentistry, University of Bristol, Bristol, UK.

[5] National Institute for Health Research Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, UK.

*Corresponding author:

Ester Carreño,

Bristol Eye Hospital,

Lower Maudlin Street,

Bristol BS1 2LX

Phone: +44 (0) 117 342 4878

Fax: +44 (0) 117 342 4721

E-mail: Ester.Carreno-Salas@UHBristol.nhs.uk

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(93 words)

The ophthalmic manifestations of dengue fever include a visually impairing maculopathy, where patients are left with a central or paracentral relative scotoma. We present a case of a 26-year old female patient returning from Thailand with unilateral reduction in visual acuity and a central scotoma associated with dengue fever. We report the use of the OCTA as a non-invasive imaging platform to demonstrate its value in showing the persistent changes corresponding to the functional central scotoma in dengue-related maculopathy, which often cannot be visualised clinically, or by standard OCT and fundus fluorescein angiography.

Introduction:

Dengue fever is a viral infection transmitted by the bite of the Aedes aegypti mosquitos,[1] prevalent in Southeast Asia, India, Africa and the American tropics.[2] The clinical severity of dengue fever can range from a mild self-limiting febrile illness to a more severe, and potentially life-threatening dengue haemorrhagic fever causing thrombocytopenia and shock. Ophthalmic complications are thought to occur in 10% of cases, and sight threatening complications in 5-8%.[3, 4] Ophthalmic complications can vary from an acute anterior and intermediate uveitis to a visually impairing neuroretinitis and macular chorioretinopathy.[3-11] The use of optical coherence tomography (OCT) patterns[11] and multifocal electroretinography (mfERG)[12] in dengue-related maculopathy offers prognostic value. With the advent of OCT angiography (OCTA), further opportunities exist to elucidate changes in dengue-related maculopathy and add to the multimodal imaging platforms to deliver improved prognostication.

Case report:

A 26-year old female, who had recently returned from Thailand, presented with right-sided reduction in vision and central visual loss, preceded by 5 days of fever. She was under the care of the medical team and was noted to have had a 2-day history of thrombocytopenia. Diagnosis of dengue fever was confirmed by PCR in serum, 20 days after initial presentation.

The onset of the visual symptoms coincided with the nadir of the platelet count. Visual acuities were 1.0 (LogMAR notation), and 0.8 with pinhole, on the right, and 0.0 on the left. Anterior segment examination was unremarkable. Fundus

examination showed a small flame retinal haemorrhage superior to the macula on the right with a surrounding area of swollen pale retina, clinically representing an area of retinal ischaemia. Spectralis OCT showed a preserved ellipsoid layer with hyperreflective dots at the level of the fovea. There was decreased thickness and increased hyperreflectivity in the inner plexiform layer, at both the fovea and slightly superior to the fovea (Figure 1). The fundus fluorescein angiography (FFA) and indocyanine green fluorescein angiography (ICGA) were unremarkable, other than masking of the haemorrhage (Figure 2). OCTA (AngioVue; Optovue Inc., Fremont, California, USA) demonstrated an irregular enlargement of the foveal avascular zone, with loss of capillary network in the internal and external retinal plexus associated with masking corresponding to the haemorrhage (Figure 3). The patient was managed conservatively, without specific treatment for the ocular features. One week later, visual acuity on the right was 1.0, and 0.6 with pinhole, and 0.0 on the left, with a persistent central scotoma on the right. Clinically the fundal examination and Spectralis OCT was now unremarkable. However, as shown in figure 3, the OCTA features of the capillary network were unchanged.

Discussion:

Standard OCT patterns have previously been reported to be of value in determining the clinical course and visual outcome in patients with ocular manifestations of dengue fever.[11] In this case, the OCTA furthered our ability to understand the pathology and offer improved prognostication. The OCTA showed an irregular enlargement of the foveal avascular zone, with loss of capillaries superiorly, in the internal and external retinal plexus. These changes

persisted even after fundal changes had improved clinically, on standard OCT and also no persistent changes observed on fundus fluorescein angiography. We suggest such persistent changes in vasculature are responsible for the persistent scotoma in dengue maculopathy.

The ocular manifestations of dengue fever include macular haemorrhages occurring most commonly, with oedema, with or without retinal perivasculitis[3]. 70% of visually symptomatic patients are thought to have a maculopathy, similar to that seen in our case, and 20% have an associated uveitis.[3] The onset of visual symptoms is thought to occur with the resolution of the fever and as in our case, at the point where the platelet count is at its lowest[5,6,8].[3] The timing between fever and the development of ophthalmic manifestations has been found to be around 7 days, and potentially indicates a patho-aetiology secondary to antibody formation and deposition of immune complexes.[3, 5, 7] The present understanding of the immunopathogenesis is that the target cells of the dengue virus includes dendritic cells, monocytes and vascular endothelial cells, and inflammatory changes through the proinflammatory mediators, interferon-γ, tumour necrosis factor-α and interleukin-2, -6, and -8, lead to vascular leakage, haemorrhage and ischaemia.[13-17]

Based on standard OCT, the three patterns of maculopathy include diffuse retinal thickening, cystoid macular oedema and foveolitis.[11] As with our case, it is recognised that whilst the structural changes seen on the standard OCT and clinically fundal abnormalities spontaneously return to normal within a few days, central/paracentral scotoma can persist.[11] Although patients usually regain

good visual function, and spontaneous recovery of dengue maculopathy is known,[18, 19] there remain patients where visual recovery is prolonged and scotoma persist for up to 2 years.[11, 12] Delayed recovery is seen in those patients presenting with foveolitis and fastest recover in those with diffuse retinal thickening.[11] Furthermore, N1 and P1 responses of the mfERG remain reduced,[12] and correspond to persistent clinical scotoma, despite normal fundus appearance and normal standard OCT and fundus fluorescein angiography. This suggests that the photoreceptors or bipolar cells may remain irreversibly damaged.[12]

Our case has highlighted for the first time, a prognostic value of OCTA through visualising the on-going abnormalities that correspond to the scotoma associated with dengue maculopathy. OCTA is a non-invasive imaging technique that generates volumetric angiography images within seconds. It shows both structural and blood flow changes, and provides a highly detailed view of the retinal vasculature.[20] In our case, the OCTA showed an irregular enlargement of the foveal avascular zone, with loss of capillaries superiorly, in the internal and external retinal plexus.

In conclusion, the use of the OCTA enables the diagnosis, visualisation and monitoring of dengue maculopathy. It provides an exciting prognostic tool for the monitoring of these patients.

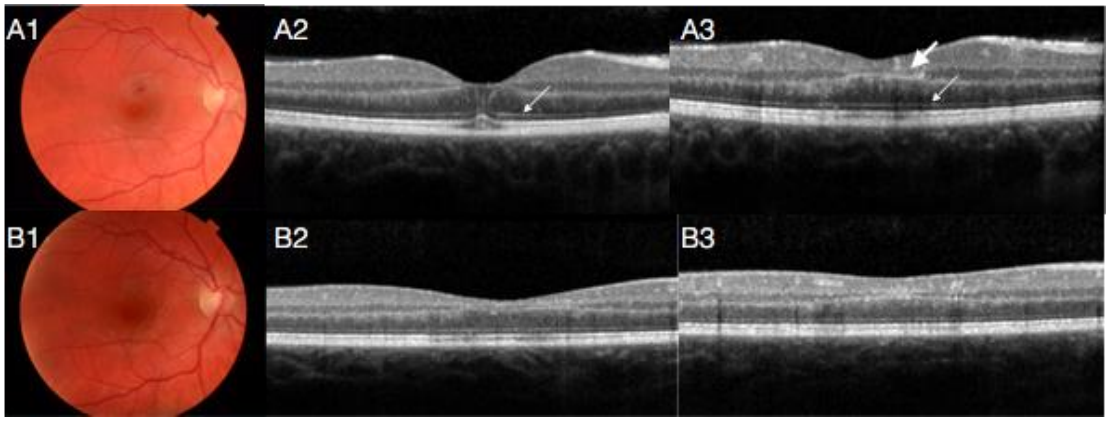

Figure 1.- Colour pictures and spectral domain ocular coherence tomography (SD-OCT) at the level of the fovea (A2,B2) and superior to fovea (A3,B3) of the right 2 days (line A) and 10 days after the presentation (line B). Disclosing a preserved ellipsoid layer (thinner arrows), and area of hypereflectivity at the level of the inner plexiform layer superior to the fovea (thicker arrow), that partially resolved in latter SD-OCT.

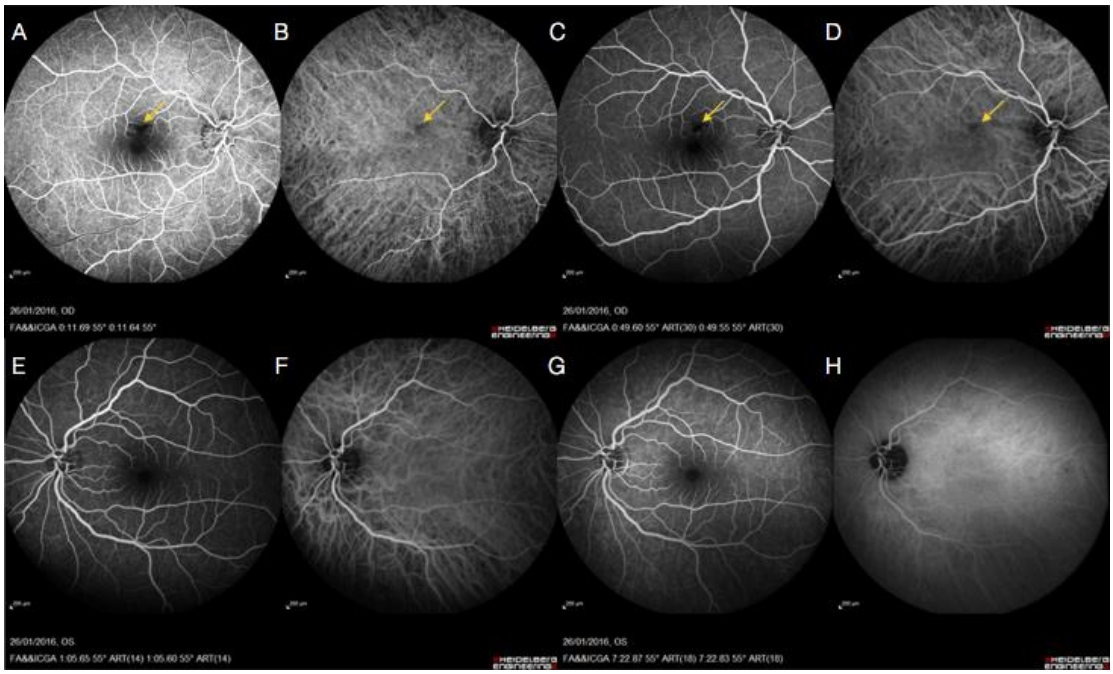

Figure 2.- Fundus fluorescein angiography (FFA) (A,C,E,G) and indocyanine green angiography (ICGA) (B,D,F,H) showing early frames (A,B,E,F) and late

frames (C,D,G,H), correspond to images of the right (A-D) and to the left eye (E-H). Right FFA and ICGA demonstrate a masking effect of flame haemorrhage superior to fovea (arrow), but no other abnormal findings.

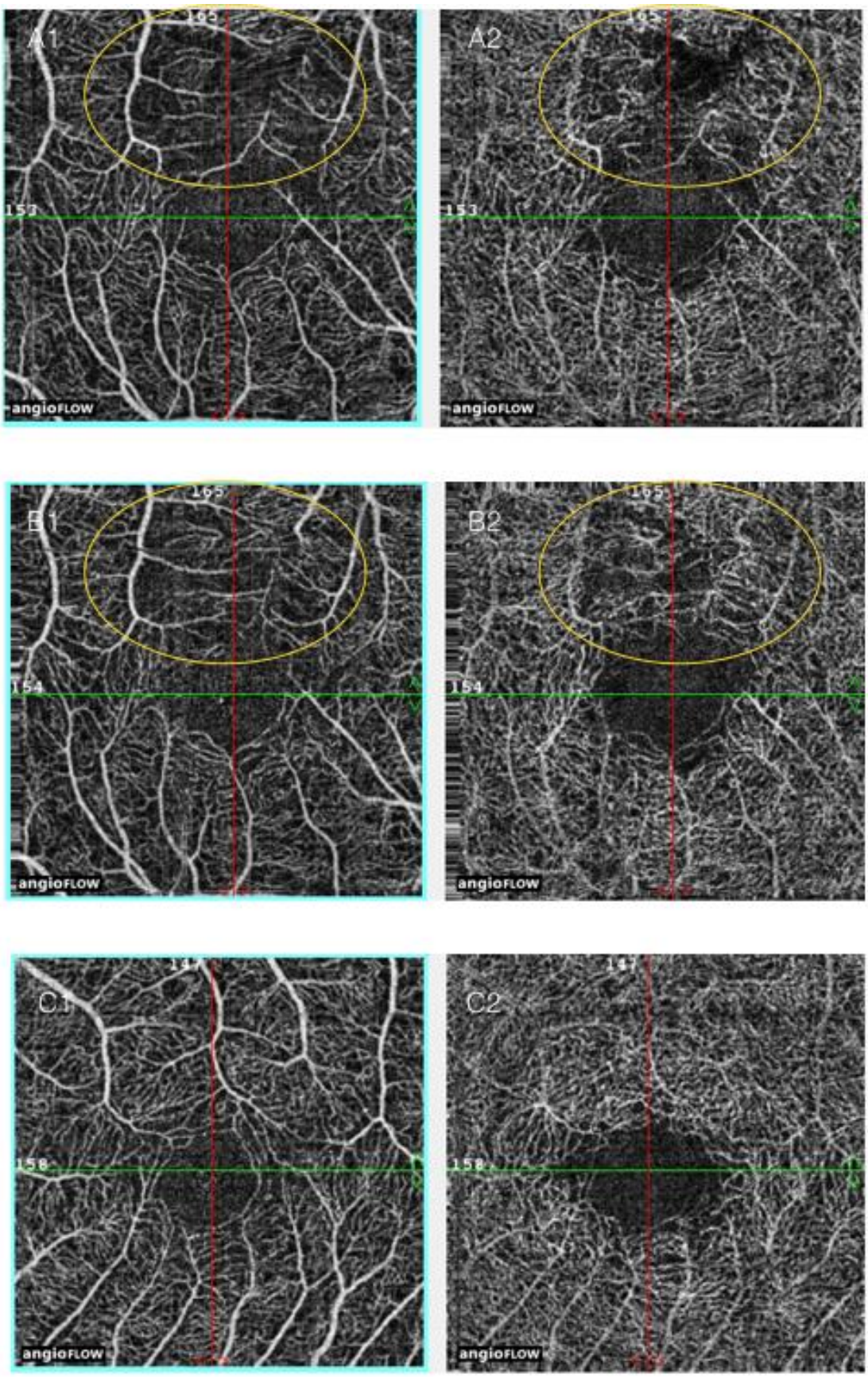
A1
A2
B1
B2
C1
C2
angioFLOW

Figure 3.- OCTA, showing the superficial (column 1) and deeper (column 2) retinal plexus of the right eye, 2 days after presentation (row A), 10 days after presentation (row B), and left eye (row C). Showing the masking effect of the retinal haemorrhage in the early images of the right eye and loss of capillary density superior to the foveal avascular zone persistent in the time present in the superficial and deeper retinal plexus of the right eye (yellow circle).

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